ORTHO
DERMATOLOGICAL

NOV 24 1999

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Rm. I-23
12420 Parklawn Drive
Rockville, MD 20857

99N-5718 99 NOV 26 AM 8:26

CITIZEN PETITION

The undersigned, Ortho Dermatological, a division of Ortho-McNeil Pharmaceutical, Inc., (ODI) submits this petition pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act (FDCA) and 21 C.F.R. 10.30 and 320.24, to request the Commissioner of Food and Drugs to take the actions and refrain from taking the actions specified below.

A. Action Requested

1. FDA should not finalize the draft guidance titled "Topical Dermatological Drug Product NDAs and ANDAs – In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies" (the "Draft Guidance"), in which a dermatopharmacokinetics (DPK) method, tape stripping, is proposed as a method of demonstrating bioequivalence, until that method is: a) validated as being a scientifically valid and reproducible method; and b) correlated to clinical safety and efficacy such that a demonstration of comparability using the DKP method between a generic and innovator product will provide adequate assurances that the two products will be, in fact, clinically similar.

2. FDA should not finalize the Draft Guidance for any one class of drug product (e.g., anti-fungal, corticosteroids, retinoids, etc.) unless and until the requirements noted above have been fulfilled for that particular class of drug products. Different topical compounds have different sites of drug action. The application of tape stripping as a measure of bioequivalence for every topical drug product, regardless of the site of action of the drug product, cannot be supported scientifically.

98D-0388

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3. FDA should not approve any generic topical drug product under an abbreviated new drug application ("ANDA") pursuant to the Draft Guidance until and unless the generic manufacturer demonstrates that the DPK tape stripping method has been validated, as noted above, and demonstrated to be an appropriate surrogate for demonstrating similar clinical safety and efficacy.

4. FDA should not permit the use, as suggested in the Draft Guidance, of In Vitro Release testing to establish BE for lower strength topical drug products where BE has been established for a higher strength topical drug product. In a consensus report of industry, regulatory and academic scientists, it has already been established that in vitro "release test is neither a surrogate test for bioavailability nor for bioequivalence and should be used only as supportive evidence in such evaluations"(Workshop Report " Assessment of Value and Application of In Vitro Testing of Topical Dermatological Drug Products, Pharm. Res.,Vol 16,No. 9, p.1329, 1999.

5. The Draft Guidance needs to specifically address the details of how to validate the tape stripping procedure and the methods used in the analysis of drug concentrations.

B. Statement of Grounds

In June 1998, FDA published in the Federal Register a guidance for Industry in draft form titled 'Topical Dermatological Drug Product NDAs and ANDAs – In Vivo, Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies (the "Draft Guidance"). In the Draft Guidance, FDA proposed to permit generic companies to use a DPK method, tape stripping, to demonstrate bioequivalence ("BE") between a generic topical product and the innovator topical products. In addition, FDA proposed that where the generic manufacturer seeks approval for lower strengths of the product involved, an in vitro release method may be used to demonstrate BE. FDA has recently announced that it intends to finalize the Draft Guidance without material changes, despite significant concerns raised by Industry and certain FDA officials that these methods of demonstrating BE have not been sufficiently validated and have never been adequately correlated to clinical outcomes.

We understand that FDA has great latitude in determining methods that can be used to establish BE. Those methods, however, must be reasonably and scientifically supported as appropriate surrogates for demonstrating comparable safety and efficacy between the generic product and the innovator; that is, that the products will truly be bioequivalent. See Scherina Corp. v. Sullivan, 782 F. Supp. 645, 651 (D.D.C. Jan. 17, 1992). In this case, there is no scientific consensus that either tape stripping or in vitro release has been adequately demonstrated to be valid methods of determining BE. In fact, there is no consensus within FDA that the methods are appropriate. FDA should not finalize the Draft Guidance until sufficient data has been generated to demonstrate that the methods are validated and will ensure that only truly bioequivalent products are approved.

1. Background

The Draft Guidance contains recommendations for the establishment of BE by the use of a DPK method, tape stripping, for all topical products, including antifungals, corticosteroids, antiacne (retinoids) and vaginally applied products. This issue has been the subject of several workshops and recently was presented to the FDA Advisory Committee for Pharmaceutical Science (PS) and the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC). Although tape stripping may be conceptually a potential method for determining topical BE, insufficient data exists, as has been noted by practicing dermatologists, and many members of the academic, industrial, and government scientific community, to permit the method to be used as a determinant of BE.

2. Summary of Concerns

The following is a summary of the scientific concerns that ODI believes call into significant question the viability and acceptability of the Draft Guidance. These concerns, as mentioned above, have been previously raised by Johnson & Johnson as well as the Pharmaceutical Research and Manufacturers of America (PhRMA). These concerns are addressed in greater detail in Exhibits 1 (Johnson & Johnson Comments on the Draft Guidance for Industry, Docket 98-D-0388) and 2 (PhRMA Comments to the Topical BE Task Force). These Exhibits are incorporated by reference into this Citizen Petition.

The concerns are: (1) There are no peer-reviewed studies that demonstrate a correlation between DPK **and** clinical safety and efficacy for any dermatological compounds; (2) There are inadequate DPK data correlating SC drug concentrations to concentrations at the target tissue (epidermis/dermis/hair follicle) or in systemic circulation validating the use of SC tissue as a surrogate for concentrations of drug at the active site; (3) There are **clear** data demonstrating that DPK may fail to predict safety and efficacy for drug products that are delivered to and through hair follicles; (4) Single dose DPK studies on the healthy adult arm will not consistently predict equivalence in diseased skin, geriatric and pediatric age groups, multiple dose conditions, or skin with permeation characteristics different from the arm; (5) The Draft Guidelines do not address whether assumptions regarding DPK's ability to predict clinical safety and efficacy hold true for combination products, especially when the active ingredients have different targets; (6) DPK is inappropriate for vaginal, nail, and mucosal products because these tissues do not have stratum corneum tissue **and (7)** The DPK model does not assess the known vehicle impact on safety and efficacy; therefore, the test product must meet qualitative and quantitative (<±5.0%) similarity requirements (the current Draft Guidance does not specify any requirements to assure that the test and reference products are qualitatively and quantitatively similar).

In addition, there are numerous concerns surrounding the validation of the DPK methodology, as there is no data that validate the proposed DPK method as a reliable, precise and accurate predictor of clinical safety and efficacy, and therefore the BA/BE for topical drugs. Specifically: (1) Skin stripping is not well controlled. There is large intra- and inter-subject variability even from adjacent sites; (2) Percent of SC removed/cm* is unknown for each site; therefore it is inappropriate to normalize drug concentration/cm*; (3) The proposed 10 strip samples represents only a small portion of the SC. Whether the amount of drug in the first ten strips truly represents SC levels, or whether the first ten strips simply represents unabsorbed drug trapped in the skin furrows has not been studied. In order to measure drug in the deeper SC layers (those closest to the viable epidermis); at least 30 strips must be removed. This can lead to pain, scarring, and hyperpigmentation. (4) It is well accepted that after topical application, there is a drug concentration gradient across the SC. This means that the amount recovered in SC samples is highly dependent on the how deep into the SC one samples (i.e. how many times the skin is tapestripped). This is in contrast to systemic blood concentrations in which the concentration of drug in the plasma or serum is homogeneous, and independent of sampling volume (or weight).

Thus, with blood levels one can standardize the amount of drug in a given sample to a standard unit, i.e. amount of drug/mL or drug/gram of plasma/serum with confidence. However, the non-homogeneous nature of the drug in the SC tissue makes it inappropriate to try to standardize drug concentration by weight of the SC. As the area sampled is held constant, standardization by area is also meaningless. Given the difficulty in data standardization to reflect the large variations in recovery observed during SC tissue sampling, no meaningful information regarding the rate and extent of absorption of reference and test drug can be obtained.

Concerning the use of In Vitro Release (IVR) approaches for establishing bioequivalence for lower strengths of approved generic products (Section D of the Draft Guidance), data presented at the Joint Advisory Committee on 10/23/99 demonstrated that using IVR as a measure of bioequivalence gave results inconsistent with clinical trial data. Specifically, comparisons of Retin-A cream to a generic tretinoin cream gave IVR profiles that were, when analyzed by standard BE metrics, not bioequivalent in an initial study, but were bioequivalent when compared in a repeat study. This inconsistency between studies was noted, despite the fact that in both studies the test and reference formulations would have been considered the “same” as defined in SUPAC-SS (Scale-Up and Post-Approval Changes - Semisolids). The lack of consistency suggests that the use of IVR approaches for approval of a lower strength generic product is not justified as a replacement for clinical trials. The inappropriateness of using IVR to demonstrate BE had previously been stated in the publication from the Workshop Report “Assessment of Value and Applications of In Vitro Testing of Topical Dermatological Drug Products” in Pharm. Res. Vol., No. 9, pp.1325-1330.

Given the issues outlined above, it is clear why no consensus within Industry or even among FDA personnel exists regarding the appropriateness of the Draft Guidance. In fact, it appears that those within FDA who are pushing for approval of the Draft Guidance may be going against the considerable weight of opinion within the scientific community. In addition to comments submitted by Johnson & Johnson and PhRMA, we are attaching, **as** Exhibit 3, comments submitted by the American Academy of Dermatology. These comments raise similar concerns with the Draft Guidance. The AAD concludes its letter by stating "The Academy continues to believe that skin tape stripping remains an intriguing, but still problematic testing method, and at this time should not be adopted as a means of assessing bioequivalence of generic dermatologic drugs."

B. Environmental Impact

The actions requested herein qualify for categorical exclusion from the requirement of issuance of an environmental impact assessment, pursuant to 21 C.F.R. 25.24(a), (c). Further, ODI does not believe that any substantial environmental impact will result from the relief requested.

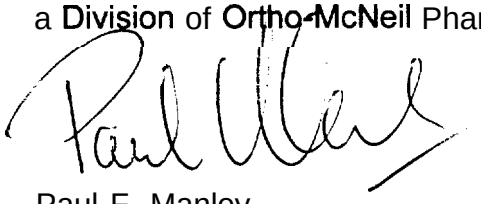
C. Economic Impact

ODI will provide data regarding the economic impact of the requested relief upon request by the Commissioner, pursuant to 21 C.F.R. 10.30(b).

D. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully yours
on behalf of Ortho Dermatological,
a Division of Ortho-McNeil Pharmaceutical Inc.



Paul F. Manley
Worldwide Director
Regulatory Affairs

Exhibit 1

Johnson & Johnson
CONSUMER COMPANIES, INC.

AUG 17 1998

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville
Maryland 20852

Re: Docket No. **98D-0388;** Draft **Guidance for Industry.**
Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies; Response to Request for Comments.

Dear Sir/Madam:

The purpose of this correspondence is to provide, on behalf of Johnson & Johnson, comments on the above Draft Guidance published in the Federal Register dated June 18, 1998 (63FR 33375).

Johnson & Johnson supports the Food and Drug Administration initiative to determine viable approaches to establishing bioequivalence for topical dermatological drug products, and applauds the efforts put into preparing this draft guidance. However, we also believe it to be imperative that all interested parties view any proposed methodology as scientifically valid and robust. At this time, we respectfully feel that the guidance has serious limitations, many of which have been raised previously by practicing dermatologists, the academic, industrial and government scientific community.

To that end, we have put forward a detailed response, with data where appropriate, for your review and consideration. Three copies of this response, with supporting data, are enclosed, including 2 desk copies for Drs Vinod Shah and Roger Williams. We would also like to request the option to present data at any forthcoming Advisory Committee or other meeting on this subject.

Should you have any questions regarding this document, or require further copies, please do not hesitate to contact me on (908) 874 1239, or our number dedicated for FDA use, (908) 874 1700.

Sincerely,

Paul F. Manley
Director
Regulatory Affairs

cc: Vinod P. Shah, PhD, FDA, CDER, (HFD-350)
Roger L. Williams, MD, FDA, CDER, (HFD-003)

Johnson & Johnson
Skillman, NJ 08558

Docket 98-D-0388

Johnson & Johnson
Comments on the Draft Guidance for Industry

Topical Dermatological Drug Product NDAs and ANDAs - In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies

Johnson & Johnson
Skillman, NJ 08558

Docket 98-D-0388

Comments on the Draft Guidance for Industry

Topical Dermatological Drug Product NDAs and ANDAs – In Vivo Bioavailability Bioequivalence, In Vitro Release, and Associated Studies

1. INTRODUCTION

The above entitled Guidance contains recommendations for the establishment of bioequivalence (BE) by the use of dermatopharmacokinetics (DPK or tape stripping) for all topical products, including antifungals, corticosteriods, antiacne (retinoids) and vaginally applied products. This issue has been the subject of several Workshops and recently was presented to the FDA Advisory Committee for Pharmaceutical Science (PS) and the Dermatologic and Opthalmic Drugs Advisory Committee (DODAC) at public meetings. Although we agree that DPK is conceptually a good methodology for supplementing data to determine topical bioequivalence, serious limitations in implementation have been raised by practicing dermatologists, and the academic, industrial, and government scientific community, which we feel have not been adequately addressed by the available data.

2. HISTORY

'The main feature of the Guidance is the use of dexmatopharmacokinetics (DPK), i.e., the measurement of stratum comeum drug concentrations in tape stripped skin, as a measure of bioequivalence. This technique was considered by academic, government and industry scientists at several workshops sponsored by the FDA and the American Association of Pharmaceutical Scientists (AAPS). In the report from the ***AAPS/FDA Workshop on in vivo Percutaneous Penetration/Absorption*** held May l-3, 1989, the advantages/disadvantages of this technique were outlined and the following issues were identified:

> ***"The correlation between the amount of drug in the stratum comeum and total drug absorption has only been established for some drugs and formulations. Since different body sites of skin have different drug penetration properties, the site of application has to be specified for predicting drug absorption like for any other method. This method does not sample the epidermis or the dermis (i.e. the normal 'targets' of topical drug products). The cleaning and preparation of the skin for stripping is a critical determinant of drug recovery".***

These issues, and others identified in subsequent Workshops and Advisory Committee meetings, have not been addressed in the proposed Guideline.

The possibilities of utilizing skin stripping methodology (DPK) were examined in September, ***1996*** at the ***AAPS Workshop on Bioequivalence of Topical Dermatoiogical Dosage Forms – Methods for Evaluation of Bioequivalence.*** As pan: of this workshop, a protocol outline for a **skin** stripping BE study was presented. Although this protocol made attempts to address some of the issues mentioned above, either no data, or preliminary, unvalidated information was presented to justify many of the procedures used, **i.e,** site of application, which tape to use, the number and size of the sites, cleaning and preparation of skin, validation of sample analytical techniques, appropriate statistical measures, etc. The protocol described in the Workshop report, however, remains the basis of the **current** Guidance.

The use of DPK as a measure of BE was also the subject of a December 11, 1997 meeting of the Advisory Committee for Pharmaceutical Science. One of the Committee's conclusions was that ***"I think that we agree*** that ***perhaps, if there are specific targets to the lower follicle. perhaps DPK may not be appropriate."*** (Transcript, pg. 108).

Another conclusion from one of the presenters, Dr. Hans Schaefer, was that ***" If ever*** you have an ***influence on the properties of the horny layer*** itself; on its barrier and *reservoir* function, it ***doesn't hold anymore.",*** and in response to the question from Dr. Lambom, "You ***'re saving that - this substitute assay would not pick-up whether or not it's bioequivalent if*** *in fact* ***the vehicles were different?"***, Dr. Schaefer replied, ***"Yes. I would say you wouldfind a difference anyway."*** (Transcript, pg. 103). As is discussed later in this response, tretinoin formulations induce changes in the stratum comeum (Effendy, et al). We therefore agree with these conclusions, and present herein the additional reasons that for certain compounds and indications, DPK methodology is not appropriate as a method for establishment of BE.

This current guidance was also presented at the 49" Meeting of the Dermatologic and **Opthalmic** Drugs Advisory Committee (DODAC) on ***Bioequivalence of Topical Dermatoiogical Drug Products*** on March 19, 1998. This committee cited lack of validation of the skin stripping technique and variability of the method. Lynn Drake, M.D., Member of the Advisory Committee, stated regarding DPK that, ***"....I am unwilling as one member....to accept this test as a replacement*** *for* ***what we actually do in patients and see in patients, ...and this test as*** *far as I am* ***concerned is still way far away from me being able to accept it as the best way to evaluate or accept judgement on equivalent drug..."*** (Transcripts, pg 139).

Another committee member, 0. Fred Miller, III, M.D., **stated that** ***"I think that (DPK).....might become the surrogate*** *for* ***antifungals, but not*** *for* ***retinoids and not*** *for* ***corticosteroids. But I think*** *in* ***this*** *infancy* ***stage and with all the variables that we have and that have been discussed, that there certainly has to be clinical correlation with what we are seeing with the DPK, and can we consistently say the DPK showed this, and this is what the clinical correlation was, and then maybe we can go forward with it."*** (Transcript, pg. 140).

The Guidance also contains recommendations for using in vitro release (IVR) technology as a measure of bioequivalence for lower strengths of topical products (Section D of this response). The recommendation that a waiver of BE studies for lower strengths by the use of IVR was specifically addressed at the ***AAPS Workshop on Assessment of Value and Applications of In-Vitro Testing of Topical Dermatological Drug Products*** (September, 1997) in which the consensus of the scientific community, as published in the Workshop report, stated that this technique was not appropriate as a measure of bioequivalence. This opinion was seconded at the recent (March 19, 1998) DODAC meeting by Jonathan Wilkins, M.D., Director, Division of Dermatological and Dental Drug Products (DDDDP). Despite these recommendations, the use of IVR as a substitute for in vivo bioequivalence studies of lower strengths of certain NDA and ANDA products is being recommended in the Guidance.

The Guidance also proposes the use of IVR as a routine Quality Control test for topical products (see Section V of the guidance). This recommendation was previously, specifically removed from the ***Guidance for Industry, Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation,*** based on a consensus of industry, academia and government scientists. To our knowledge, there has been no additional data made available to support a change in policy on this issue.

1. SPECIFIC COMMENTS ON THE DRAFT GUIDANCE

We have the following comments on specific items in the Guidance which are presented in the order they appear in the document.

Section II. BACKGROUND

We agree with the statement that ***"For topical dermatological drug products, PK measurements in blood, plasma, and/or urine are usually not feasible to document BE because topical dermatoiogic products generally do not produce measurable concentrations in extra-cutaneous biological fluids. The BA/BE determination for these products is thus often based on PD or clinical studies."*** However, in view of the comments which will follow in this correspondence, we feel it necessary to emphasize that the subsequent statement within the draft guidance, ***"An additional approach considered in this guidance is to document BA/BE through reliance on measurement of the active moiety(ies) in the stratum corneum. This approach is termed dermatopharmacokinetics (DPK)"*** should be interpreted in such a fashion that data could only be considered as potentially supportive in complementing efficacy data from at least one adequate and controlled clinical trial comparing the ANDA product to both placebo and the reference listed drug (RLD). As our response outlines, DPK data has not been proven thus far to be a reliable and reproducible marker for BE of all topical drug products, and as such cannot be regarded as a valid methodology to be utilized on its own for such determinations.

Section III. INACTIVE INGREDIENTS

We are in agreement with the statement confirming that an ANDA may not be approved in circumstances where preclinical or clinical studies are needed to demonstrate the safety of inactive ingredient(s). In particular, there has been at least one circumstance where an applicant has filed ANDAs for formulations which included novel excipients not included previously in pharmaceuticals. In that case, the presence of the novel excipient prompted Agency requests for the applicant to tile a modified NDA (a 505(b)2 application), which included at least one adequate and controlled clinical trial against placebo and the RFL. This allowed the approved product to ultimately be rated AB bioequivalent. Therefore we strongly support the need for such products to he supported by data from nonclinical studies as well as clinical safety information.

Section IV. BIOAVAILABILITY AND BIOEQUTVALENCE

A. Clinical Trials Approaches

We agree that clinical trials for topical bioequivalence are hard to perform, highly variable and insensitive. However, we also agree with the comment from S. James Kilpatrick, Jr., Ph.D. during the DODAC Advisory Committee meeting of March 19, 1998 that ***"I am suggesting, like other members*** *of* ***the committee. that we should look*** *for* ***more information on the conformability or coherence between clinical results and DPK results...I feel we need more information before we can*** let ***DPK fly on*** its own. **"** (Transcript, pg 146).

B. Dermatopharmacokinetic Approaches

Currently there is little or no data to support the DPK approach for establishing bioequivalence. The DPK methodology makes a number of assumptions based on the way bioequivalence is established for orally administered drugs. One such assumption **is** that the stratum comeum is an appropriate dose **surrogate** for target site tissues in the skin. Another assumptiion is that we can compare the amount of drug in the tape strips vs. time data to perform phannacokinetic analysis of SC concentrations, as is routinely done with plasma concentrations after oral administration. However, many years of study have shown that the use of blood concentrations as a surrogate for target site concentrations for establishing oral BE is an acceptable approach, presumably due to the fact that the concentration of drug in the plasma is in equilibrium with the organs that are the site of activity. For topical drug products, no such equilibrium has been shown to exist. We challenge these assumptions based on the results of studies conducted by Johnson & Johnson which will be discussed below and for which full reports of the experiments are given in the attached Appendices.

In light of the lack of available data. one of the main questions that has been consistently raised about the use of DPK for determination of topical bioequivalence has been whether stratum comeum drug concentrations can be correlated with clinical efficacy. To date, no such clinical studies are available. If the amount of drug in the tape strips is expected to predict clinical outcome, then two key questions arise: First, is drug content in the tape strips indicative of drug content in the stratum comeum? Secondly, are stratum comeum concentrations correlated with the concentration of the tissue at the target site? The ultimate answers to these questions would require one to conduct a clinical pharmacokinetic study in which skin sections were collected, drug (and active metabolites) content for stratum comeum and target tissue (i.e. epidermis, dermis, sebaceous gland. and/or hair follicles) was determined, and the data analyzed to see whether they correlated in any acceptable fashion. Such a study is difficult to conduct because of the need for biopsies, as well as the low concentrations of drug at the target sites, which often require the use of radioactive tracers (Jamoulle and Schaefer, 1993).

Therefore, in order to provide some scientific rationale for the DPK approach, several different types of studies have been cited in the Draft Guidance. In one study, a correlation was found between the amount of compound in the stratum comeum of hairless rats 30 minutes after dosing with the amount of drug ***predicted*** to be ***absorbed*** in these animals (Rougier and Lotte, 1993). - This correlation was shown under the ideal conditions of the study, i.e., for **hydrophilic,** permeable compounds in simple vehicles of maximum solubility.

It has been noted that ***". . . .it (DPK) has not yet been accepted or recommended by the regulatory agencies in bioequivalence determination, possibly because*** *of* ***its apparent limitations in the area*** *of very* ***lipophilic drugs (e.g., retinoids or antifungals such as ketoconazole), where the quantity measured is too*** low***".*** (Jamoulle and Schaefer, 1993). Even for the model compounds used in the aforementioned study, (caffeine, benzoic acid, acetylsalicylic acid) ***in*** vivo human studies indicate that under ideal conditions the correlation between amount of drug in the stratum comeum and "predicted" percutaneous absorption is low (r=0.7) (Rougier and Lotte, 1993). It should also be noted that the DPK method as used above was a surrogate for **systemic** absorption, and not for the concentration of drug (and/or active metabolites) at the possible target sites in the skin. As stated on page 3 of the current Draft Guidance ***"Although measurement*** *of* ***the active moiety(ies) in blood or urine is not (emphasis added) regarded as an acceptable measurement*** *of* ***BA/BE*** *for* ***dermatological products, it may be used to measure systemic exposure."*** Thus, while the work of Rougier cited in the Guidance may support the use of DPK as a surrogate for absorption (for the compounds and conditions studied), it does not provide any information on whether a correlation exists between stratum comeum concentrations and those in the epidermis, dermis, pilosebaceous glands, hair follicle or any other skin appendage that may be a site of action for dermatological products.

In order to address the issue of whether stratum comeum tissue concentrations, as assessed by the amount recovered from tape strips, is an appropriate surrogate for dermal and epidermai tissues, an investigation was conducted with human skin in vitro This commonly used model was used in lieu of a clinical study due to the technical/ethical issues such as use of a radiolabeiied tracer or the need for biopsies as discussed previously. A full report of the results of these studies, which were presented at the September, 1996 ***AAPS Workshop on Bioequivaience of Topical Dermatological Dosage Forms – Methods for Evaluation of Bioequivalence*** are presented in **Appendix A.** This work also examined the effect of minor formulation and manufacturing changes on the profile of retinoid concentrations in the various tissue layers. The results of these studies clearly showed that there is no linear correlation between the amount of compound in the stratum comeum tissue and the amount in the epidermis, dermis, or combined dermai and epidermai tissue (r= 0.02-0.66) at the time points investigated. In addition, minor changes in manufacturing and/or the formulation were found to alter concentrations in the different skin compartments, but the changes seen in the tape strippings were not correlated with changes found in other tissues. These studies concluded that one cannot, therefore, use the stratum comeum concentrations to predict what is in the epidermis or dermis (the target site for many dermatoiogicai products).

The Guidance does recognize that antifungals are the only topical product for which the stratum comeum may be a site of action and for which DPK methodology may be considered to be an appropriate way to sample target site tissue. This was acknowledged by both Advisory Committees and the Draft Guidance states: ***"For antiacne drug products, target sites are the hair follicles and sebaceous glands. In this setting, the drug diffuses through the stratum comeum, epidermis, and dermis to reach the*** site *of* ***action. The drug may also follow follicular pathways to reach the sites*** *of* ***action."*** Despite this, the Draft Guidance continues to support the use of stratum comeum drug concentrations in lieu of target site tissue, and states". . . ***the DPK approach is still expected to be applicable because studies indicate a positive*** *correlation between stratum* ***comeum concentrations and follicular concentrations."*** No details or references are given to demonstrate this important correlation. It is not known therefore whether this correlation was shown in animals or humans, in vivo or in vitro, and whether it may be applied, as is suggested in this Guidance, universally to ail dermatoiogicai compounds. We question the validity of such a statement without adequate and substantial supportive scientific data.

In addition, no experimental evidence is referenced that would validate this guideline for vaginaiiy administered products. The Draft Guidance states that, ***"... DPK principles should be generally applicable to all topical dermatological drug products including antifungal, antiviral. . . . . and vaginaiiy applied drug products "***. The guidance goes on to say that, ***"A DPK approach is not generally applicable . ...3)*** *for* ***ophthalmic preparations because the cornea is structurally different from the stratum comeum "***.

The following presents evidence that the DPK approach cannot be utilized for vaginally applied drugs for similar reasons.

(i) Skin is quite different from vaginal mucosa. both structurally and biologically (Table I, Osborne et al, 1990; Burgos et al, 1978), most notably because of the absence of stratum comeum. As opposed to skin, where stratum comeum presents a barrier to penetration of drug and a drug reservoir, vaginal mucosa is a hormone-sensitive, vascular, highly absorptive structure. Because of these differences, it would, of course, be inappropriate to predict the delivery of a topically acting drug to vaginal mucosa, based on its delivery to stratum comeum. Determining equivalence through stratum comeum stripping may not be sufficiently sensitive to discriminate two products which could possess different absorption profiles from the vaginal mucosa. This could represent a safety issue in that a product determined to be equivalent by stratum comeum stripping could be absorbed much more readily from the vagina, compared to its "equivalent" comparator, resulting in unsafe systemic levels of drug. Stripping the vaginal mucosa in the same fashion as stratum comeum is not likely to be predictive of equivalence and would be fraught with difftcuity and considerable pain. Thus, for the same reasons that ophthalmic preparations are excluded from this guidance, vaginaiiy applied drugs should also be excluded.

Table 1. COMPARISON OF SKIN STRUCTURE vs. VAGINAL MUCOSA

SKIN			VAGINAL MUCOSA (no stratum comeum)		
Layer	Structure	Function	Layer	Structure	Function
Stratum comeum	Non-viable keratin-filled cells (squames) with bilayer-structured lipids fill between the intercellular space.	Provide a barrier against the permeation of most substances	Superficial zone: Superficial layer and Transitional layer	The superficial zone contains squamous cells which reach maximal thickness at ovulation	Forms the outer layer of the vaginal mucosa
Viable epidermis	Lie below the stratum comeum and consists of stratified keratinizing epithelial cells: does not contain blood vessels; rely on nourishment by cell Ruid from the deeper dermis layer	Produce stratum comeum	Intermediate layer	Round or irregular shape; increase in volume toward the ovulation time when the intermediate layer becomes the thickest layer of the epithelium.	Produce superficial zone
Dermis	Consists of dense, irregularly arranged connective tissue: nourished directly by blood vessels.	Provide cell fluid to the viable epidermis	Parabasal layer	Has several layers of polyhedral cells with distinct nuclei.	Proliferative compartment
			Basal layer	Has a single row of cuboidal cells overlying tha basement membrane.	Proliferative compartment; contact with blood vessels

[ii) Vaginal fluid and mucosa are significantly different chemically, compared to stratum comeum (Osborne et al, 1990; Burgos et al, 1978; Benziger et al 1983; Park et al, 1979). The suggested method for bioequivalence testing may not be sensitive enough to detect important differences in vaginal formulations. For drugs applied to the skin, the stratum comeum is the rate limiting barrier. The partitioning of the drug from the formula into the stratum comeum, as expressed by the ratio of the drug solubility in the formula and stratum comeum is the key to optimizing a formulation. For vaginally applied drugs the partitioning of drug from the formula into vaginal fluid and then from vaginal fluid into vaginal mucosa are key to optimizing delivery (Benziger et al, 1983; Park et al, 1979). Thus the chemical properties and volume of vaginal fluid, as well as the chemical properties of vaginal mucosa are important.

(iii) There is currently no validated method to determine bioequivalence through proxy vaginal measures. Investigators have utilized vaginal swabs, or vaginal scrapings in an attempt to determine levels of drug in vaginal tissue (Odds and McDonald, 1981). However, the body of work needed to correlate these values to clinical cure has not been performed and there is a great deal of variability in the results.

(iv) Since efficacy of locally acting drugs (such as antifungal treatments for vulvo-vaginal candidiasis) is a combination of microbiological cure and improvement or elimination of signs and symptoms, the delivery of drug to the diseased tissue is only part of the equation. The concomitant application of an emollient formulation to the inflamed tissue, can have an impact on elimination of symptoms. Thus the overall cure rate will be affected by the type of formulation (e.g., emollient cream, emollient suppository or solid insert, with or without vulvar cream). Again, a demtatologic model may not be sufficiently sensitive to discriminate between two different vaginal formulations.

(v) Utilizing systemic bioavailability data to predict cure of locally acting drugs suffers from other limitations. The ideal vaginal formulation would deliver high local levels of drug with minimal systemic absorption. No data correlate systemic levels with local effect. Additionally, them has recently been a question of whether vaginal administration of drug results in high levels of drug at the uterus, compared to systemic administration.

1. Performance and Validation of the Skin Stripping Technique

We agree with the guidance statement that, *"DPK studies should include validation of both analytical methods and the technique of skin stripping.",* and support many of the recommendations made in this section regarding *". . ..considerations for performing the skin stripping technique. "* However in addition to some of the considerations outlined, we have demonstrated that there are numerous other issues that need to be addressed in the validation of the tape stripping procedure. The results of these studies were originally presented at the ***AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms – Methods for Evaiuation of Bioequivalence*** (September, 1996) and at the March 19, 1998 DODAC Public meeting.

In brief, these studies examined some of the parameters that may be important in the validation of the tape stripping assay, and determined how methodological issues in this technique may affect the pharmacokinetic analysis. These investigations revealed that even under rigorously controlled conditions, the process of applying and removing the tape strips leads to wide inter-subject and intra-subject variability in the amount of stratum comeum that is recovered. This variability is due to several factors: inherent variability in individual skin type and variability in stratum comeum thickness at different anatomical sites of a given individual, inherent variability in the application and removal of the tape by different "operators", and variability related to the tape selected and environmental conditions. it is clear that such variability would only be increased in skin stripping studies conducted in a multi-center fashion.

This variability in tissue recovery has important implications in the pharmacokinetic analysis of the data obtained using this method. Unlike concentrations in the blood stream, drug content in the stratum comeum is not homogeneous, but rather forms a gradient through the skin. When a standard number of tapes are removed, one does not know what percentage of the stratum comeum tissue (and drug) has been recovered in the tapes. For some individuals it may be 25%, while for others it may be 2 or 3 times that amount. In order to do pharmacokinetic analysis, the amount of drug would have to be standardized or normalized in order to construct a meaningful concentration vs. time plot. Expressing the data in amount of drug per mg of stratum comeum tissue, as is suggested in the draft guidance, would not take into account the varying percentage of drug that is recovered from the site. For example, if 25% of the total drug amount in the tissue is recovered in 3000 ug of tissue from one site, we cannot assume that 50% is recovered in 6000 ug of tissue from another site because of the lack of homogeneity in the stratum comeum sample. The effect of the unknown recovery on the concentration vs. time plot is to distort the shape of the plot. Without an accurate measure of drug concentration, no meaningful information on the rate and extent of absorption can be obtained from the pharmacokinetic plot.

The results of this study are consistent with the results of work presented by Dr. S. P. Shrivastava entitled "Validation of DPK Methods and Standardization of Bioequivalence Protocol." at the aforementioned ***AAPS Workshop on Bioequivalence of Topical Dermatoiogical Dosage Forms – Methods for Evaluation of Bioequivalence*** (September, 1996). in this study, conducted with multiple concentrations of tretinoin products (0.025 – 1 .0%), inter-subject and inter-site variation in amount of tretinon recovered was high. For example, there was a 7 fold (650%) difference in drug recovered in one subject from one site on the forearm to another (exact site not specified). The importance of a single person or "operator" doing the application and removal of the tape was highlighted by the finding that the profiles attained with a dose of 0.05% by one technician were similar to that obtained by another technician with the 0.025% dose. Based on this data obtained with topical tretinoin formulations, it was concluded that the following were "critical considerations in the standardization of a bioequivalence protocol":

- ***Stability of drug under testing and sample storage conditions should be determined.***
- ***Number of tape strips required to remove excess drug should be determined***
- ***Number of tape strips required to remove over 85% of drug from stratum corneum should be determined***
- ***Drug application, excess drug removal, and drug desorption procedures should be validated,***
- ***Drug amount-time profiles should be plotted. A standardized unit, e.g. ug/sq cm should be adopted***
- ***DPK parameters including LA UCs, LCmax (ss), Tmax (ss), T-half; etc should be calculated.***

As suggested above, one answer to the variability in drug recovery noted above may be to strip the entire stratum comeum, thereby assuring 100% removal of the drug, or at least 85% as recommended at the 1996 Workshop. In this scenario the amount of skin recovered would not be relevant. However the tape stripping process is a mildly invasive one and the amount of discomfort increases as one penetrates deeper into the stratum comeum. As presented at the March 19, 1998 DODAC Advisory Committee meeting by Dr. Latriano of Johnson & Johnson, a photograph **(see Appendix B** of this response) of sites of the forearm from several subjects shows that after the skin is stripped, there may be some redness in the area, which, after a period of time becomes hyperpigmented; in some subjects this hyperpigmentation can last for weeks or months. This further limits the feasibility of DPK methodology.

Pilot Study

The recommendations in the pilot protocol as to number of subjects, sites, timepoints, etc. have not been shown to address the above considerations. The pilot protocol also suggests the establishment of a dose-response relationship using a "simple drug solution" to show the method is validated for use with the drug product. Due to the very different types of release that may be expected with a solution vs. a more complicated drug formulation, Section III B of the Guidance indicates that a ***"topical solution drug product should be considered independently."*** This is supported by published results indicating ***"However. use of the dilution methods to create a dose-response has the inherent danger of altering the physicochemical parameters of that drug in the vehicle, which may alter drug release from the vehicle, drug uptake into the stratum comeum. and the drug activity in the skin (Pershing, et al, 2994).*** We agree that these two types of products have different characteristics and feel it is inappropriate to suggest that the results obtained with a drug in solution should be presumed valid for a semisolid preparation.

2. DPK Bioequivalence Protocol

a. Protocol and Subject Selection

The protocol calls for using healthy volunteers. It has been amply demonstrated that topical drug absorption and distribution is different in healthy vs. diseased skin (Wester and Maibach, 1992). Although using healthy subjects might be appropriate for oral BE studies, where the factors that determine rate and extent of absorption may not be affected by the diseased state, this is not true for percutaneous absorption. The stratum comeum is a major barrier for absorption of many topical products and whether the stratum comeum is impaired will have a major effect on the rate and extent of absorption of topical dermatological products that may not be captured using healthy skin. Also to be considered in subject selection is the age, gender, and skin type of the subjects. These and other variables have been shown to affect the amount of stratum comeum removed during the tape stripping process (Reed, Ghadially and Elias, 1995; Kompaore et al, 1993).

b. Application and Removal of Test and Reference Products

We agree that an SOP must be developed and validated on the application and removal of test product. as this procedure has a large influence on the reproducibility of **the** study **(Appendix B).** The recommendation calls for removal of "certain oily preparations such as ointments" by "washing with a mild soap". It has been shown for a lipophilic pesticide (alachlor) that the addition of soap reverses the partitioning of this compound into the stratum comeum (Wester and Maibach, 1992). Any procedure involved in the removal of test product needs to be validated to show that only excess drug at the stratum comeum surface is being removed and that the procedure does not affect drug concentrations in the stratum comeum.

c. Sites and Duration of Application

The recommendations in this section do not address the intra- and inter-subject variation in the amount of skin removed during the tape stripping process. Based on **the data** shown in **Appendix B,** the intra-subject variability, whether from one site to another, or from one arm to the contralateral arm, may be considerable and cannot be predicted. Also, from the data presented in **Appendix B,** the variability in the amount of skin collected (and therefore in drug concentration) - is not due to biological variation, but from variation in the recovery of the drug from the skin. This variation in tissue recovery affects the reproducibility and accuracy of the measurement of drug concentration, and cannot be eliminated by randomization of the sample sites.

d. Collection of **Sample**
and
e. Procedure for Skin Stripping

No information supporting the validation of the skin stripping procedure and the sample collection scheme has been presented. No data has been shown that supports the premise that all excess drug is removed in the first one or two strips. The data presented in **Appendix B** indicated that with 10-12 tape strips only a small fraction of stratum comeum tissue is removed. This data also show that the amount of stratum comeum removed with 10-12 strips can vary tremendously from person-to-person and site-to-site. The data in the attached study is consistent with published data where it was shown that after stripping with ten strips of 3M Tape the amount of stratum comeum removed can range from approximately <5% - 30% (Van Der Valk and Maibach, 1990). In order to recover >85% of the stratum **corneum** tissue (as recommended at the 1996 DPK workshop), one needs to reach the point of **barrier** disruption, which can require 30-67 tape strips, depending on the subject's skin type (Reed, Ghadially and **Elias,** 1995). In addition, the vehicle affects the stripping properties of the skin and it has been concluded that "the effect of vehicle treatment on stripping properties precludes one from determining drug and vehicle concentration gradients in the stratum comeum at different treatment times by direct comparison of corresponding strips.*' (Tsai, et al, 199 1).

The important question of normalization of the amount of skin obtained has not been addressed. The Draft Guidance calls for expressing the data in amounts/area. As a standardized area is being used, the denominator of area fails out of the equation, so this approach does not address this issue. We concur with the recommendations made by Dr. Shrivastava that at least 85% of the drug should be recovered. As indicated above, this would require >24 strips as used in the validation study presented in **Appendix B.** Removing that amount of stratum comeum produces a post-inflammatory response, which may be followed by hyperpigmentation of the area as shown in the photograph in **Appendix** B. We therefore question the statements that this technique is "minimally invasive".

3. Metrics And Statistical Analyses

No data has been presented that shows which are the appropriate metrics upon which to base a BE determination for topical products. No discussion around the criteria for BE has been made to determine whether the statistical criteria put forward has a relevance to clinical outcome, or in our ability to determine a formulation that may be predicted to be bioequivalent, but which fails in the clinic.

C. Pharmacodynamic Approaches

The Draft Guidance suggests a pharmacodynamic approach to establish bioequivalence may be acceptable. Specifically the guidance states that ***"Topically applied retinoid produces transepidermal water loss that may be used as a pharmacodynamic measure to assess BA/BE."***

This approach to establishing BE for retinoids, in particular for tretinoin, was addressed at a FDA Advisory Committee on September 13, 1994. At this meeting Gary Grove, Ph.D, presented to the Committee the results of a study conducted at the K.G.L. Skin Study Center that demonstrated that transepidermal water loss (TEWL) is an accepted measure of irritancy potential, but that irritation was not a reliable predictor of efficacy. This conclusion was based on a facial tolerance study that compared 0.1% RETIN-A® Cream to an experimental 0.1% aqueous gel formulation. In this study a bilateral, paired comparison between left and right side of the face in 25 volunteers, selected for sensitive skin, was made after 14 days of treatment. At the end of the treatment period, the TEWL value for the subjects treated with 0.1% RETIN-A cream was 30.8 g/m^2 compared to 22.0 g/m^2 for the subjects treated with the experimental 0.1% aqueous gel. This is in contrast to the placebo-controlled clinical studies with these two formulations (conducted separately), in which there was a similar percentage of subjects improved (reduction in overall lesion count) relative to the placebo.

Transepidermal water loss measurements were also used by Penederm to compare their tretinoin formulation (Avita™) to RETIN-A (Penedetm Summary Basis of Approval – Page 39-40 of Biophatmaceutics Review for NDA 20-404). In these studies, Penedetm compared their product to RETIN-A at the same strengths in the same type of formulation (i.e. cream and gel products). Although the two different Penederm formulations gave identical TEWL values when compared head-to-head to their Retin-A counterpart, in a clinical bioequivalence study of these Penederm products vs. RETIN-A, it was demonstrated that only the Penederm cream product was bioequivaient to the innovator. These results clearly indicate the inability of TEWL measurements to distinguish between two formulations that had different clinical outcomes.

These findings are consistent with others that support the inability of TEWL measurements to distinquish between compounds as well as formulations. In a study entitled "Functional Changes in Human Stratum Comeum Induced by Topical Glycolic Acid: Comparison with All-trans Retinoic Acid" (Effendy, et al, 1995), it was found that the plot of TEWL values over the eleven days of treatment with 12% glycolic acid in water was superimposable over the plot of obtained with 0.1% retinoic acid in ethanol. From this data one can conclude that these two compounds have a similar ability to alter the stratum comeum and that TEWL, as a measure of stratum comeum integrity, was unable to distinquish between them.

D. In *Vitro* Release Approaches (Lower Strength)

This current Draft Guidance ignores the following points of consensus which were reached in the ***Workshop on the Assessment of Value and Applications Of In-Vitro Testing of Topical Dermatoiogical Drug Products*** (September, 1997):

- ***"The release test is not a surrogate test for bioavaiiability nor bioequivaience and should only be used as supportive evidence in such evaluations."***
- ***"The in vitro release test*** is ***of no use for comparing fundamentally different formulations (ointments vs: creams, etc.)."***
- ***"In vitro release is formulation dependent and therefore should not even be used in comparisons of similar formulations made by different manufacturers. Rather, the meaningful use*** *of* ***the release test is for showing that the fundamental properties*** *of a* ***formulation of given content and manufacturing method have essentially been maintainedfollowing a SUPAC-SS-defined level I or level 2 change in the formulation."***
- ***"There is no universal release testing procedure and no universal test conditions which are applicable to all dosage*** *forms.* ***Rather, the release test must be tailored to individual drug*** *delivery formulations."*

Again, since that meeting, where a clear consensus was reached, we are unaware of any new, valid, substantial scientifically accepted data generated to refute these issues.

Within the proposed Draft Guidance it is stated that it is possible that the release rates from the test formulations are slower or faster than those of the reference formulations. The only criteria that the formulations are expected to meet is that the ratios of their release rates are similar at a given concentration. The Draft Guidance also assumes that the physical form of the drug remains constant at varying concentrations. However, it is also possible that drug in a test formulation may exist as suspended solid and in a saturated solution at higher strength, while at the lower strength, the drug may exist only in solution. The theoretical basis for release kinetics would be different and a valid comparison could not be made between high and low strength versions.

Given the possibility that the physical form of the active ingredient may differ from one strength to another, and may exhibit different release profiles, then the current Draft Guidance is inconsistent with the SUPAC-SS Guidance due to the possible effect an excipient may have on release rate. The SUPAC-SS Guidance states that if there is a change in the amount of any excipient >10% (of that present in the marketed product), then this Level 3 change would require a bioequivalence study to be conducted. The current Draft Guideline would allow a company who had demonstrated bioequivalence with a 0.1% formulation to obtain a waiver for a 0.05% or 0.025% product. This would mean a change in the active ingredient of 200-300% would be essentially deemed equivalent to a Level 1 and Level 2 SUPAC change (no bioequivalence study required). As indicated in the consensus statement above, this was not an intended use for in vitro release.

As indicated in the current Draft Guidance there is also no expectation that the innovator and generic will have similar release profiles. The only criteria would be to show similar ratios at different strengths. This criteria can result in the following clinical outcomes: If the generic formulation releases at a lower rate (the example cited in the Draft Guidance) than although it may have shown bioequivalence at the highest strength, it may fail to be clinically effective at the low strength. This is because the lower release may result in drug concentrations too low to be considered clinically effective. If the DPK test alone were sufficient to establish BE; in the instance where the generic has a faster release rate than the innovator, and efficacy was demonstrated at the high dose, the higher drug concentrations that may be produced by the generic may produce a safety problem that was not observed with the innovator. Since classic in vivo clinical BE testing would no longer be performed, the Agency would not be able to monitor adverse events in a clinical setting and may therefore fail to identify a product that has a significantly different safety profile.

Section V. IN VITRO RELEASE: EXTENSION OF THE METFIODOLOGY

This section includes a statement that ***"With suitable validation, in vitro release may be used to assess batch-to-batch quality..."*** This statement does not agree with the consensus reached at the aforementioned September 8-10, 1997 AAPS/FDA Workshop which ***states*** "***Though it provides an indication of the sameness, or lack thereof, of different batches of a given semisolid product, the release test does not appear to be sufficiently discriminating to function as the sole measure or even the principal measure of batch-to batch product consonance."***

Furthermore, for semisolids where the drug is completely in solution, the Workshop concluded, ***"While the theoretical principles associated with release testing of semisolid suspensions (drugs in suspension) are well established, more work is needed to reach the same level of understanding of semisolids which have their drugs completely in soluion."***

With these comments in mind, it is hard to envision, without substantial new supportive data, extending the applicability of In Vitro Release methodology.

Section VI. SYSTEMIC EXPOSURE STUDIES

The DPK approach proposes only to measure target site concentrations indirectly by assessing stratum comeum concentrations. This approach does not take into account systemic exposure, which, for topical products, is an assessment of a product's safety. The importance of the safety assessment for formulations of existing products that are are not equivalent in terms of Q_1 and Q_2 is demonstrated by routine expectation from the Division of Dermatological and Dental Drug Products (DDDDP) that percutaneous absorption studies would be conducted to support NDA approval. We feel that withcut an assessment of the safety of a new formulation there can be no true "risk/benefit" assessment for generic comparator drugs. Therefore, it is appropriate to expect generic formulations to meet similar criteria in this regard.

4. CONCLUSION

Johnson & Johnson supports the Food and Drug Administration initiative to determine viable approaches to establishing bioequivalence for topical dermatological drug products, and applauds the efforts put into preparing this draft guidance. However, we also believe it to be imperative that ail interested parties view any proposed methodology as scientifically valid and robust.

Although we agree that DPK is conceptually a good methodology for supplementing data to determine topical bioequivalence, serious limitations in implementation have been raised by practicing dermatologists, and the academic, industrial, and government scientific community, which we feel have not been adequately addressed by the available data.

Similarly, despite numerous recent workshops in which In Vitro release methodoiogy has been shown by consensus to be applicable, both as a research tool and as a means of assuring product sameness within SUPAC-SS, this draft guidance elevates its usefulness to other applications that are not supported scientifically.

At this time therefore, we respectfully feel that the guidance, although a good initial step, has flaws which would make it invalid for adoption. We are anxious and willing to partner with FDA and other relevant scientific bodies to investigate these and other alternate methodologies further, to achieve a final document that can be acceptable to all concerned.

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Exhibit 2

Thomas X. White
Associate Vice President
anufacturing and Quality Control
Scientific and Regulatory Affairs

PhRMA

August 24, 1999

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation
and Research
Food and Drug Administration

Vinod P. Shah, Ph.D.
Chair, Topical Dermatological
Drug Products Working Group
Center for Drug Evaluation
and Research
Food and Drug Administration

Re: Draft Guidance for Topical Dermatological Drug Products -In-Vivo Bioavailability, Bioequivalence, In-Vitro Release and Associated Studies; Draft Biopharmaceutics Coordinating Committee Background Document of May 24, 1999 for Expert Panel Review on August 27, 1999.

Dear Drs. Williams and Shah:

PhRMA representatives on the FDA's Expert Panel have reviewed the subject draft background materials and with the assistance of PhRMA's Topical Drug Product Task Force have prepared the attached evaluation report for this important topic.

Please make the attached Executive Summary and Report available to the Expert Panel as it considers the many difficult issues presented by the June, 1998 draft guidance, the unresolved issues from the October, 1998 Joint Advisory Committee Meeting and the May 24, 1998 draft background document made available for Expert Panel consideration.

On behalf of PhRMA, we appreciate the opportunity the FDA has provided for member firm representatives to participate on the Expert Panel.

Sincerely,

Thomas X. White

Attachments

cc: Jonathan Wilkin, FDA; Prakash Parab, Bristol-Meyers Squibb; Joel Sequiera, Schering-Plough; and Eric Sheinin, FDA

PhRMA TOPICAL DRUG PRODUCT TASK FORCE REPORT
ON FDA PROPOSED REVISED DRAFT GUIDANCE
MADE AVAILABLE ON MAY 24, 1999 FOR EXPERT PANEL REVIEW
AUGUST 24, 1999

Executive Summary

The following is a summary of the issues and concerns surrounding the proposed FDA document (dated 5/24/99) on Topical BA/BE which surfaced during the Joint meeting of the Pharmaceutical Sciences and DODAC Advisory Committee meeting of 10/23/98.

1. Does not address the goals and objectives **Dr. Roger Williams** outlined during the 10/23 meeting.

. *"What assumptions are* we *willing fo* make *in terms of surrogacy? Are we willing to rely on this exposure metric in the* stratum *corneum (Ref 1, pg 14)*

The current FDA proposal makes the following assumptions and hypotheses about DPK:

- two products exhibiting similar exposure patterns in the intact stratum comeum (SC) will deliver the drug at the same rate and extent to the site(s) of action in patient with dermatological disorders.
- appearance and disappearance of active drug substance in the stratum corneum will adequately reflect bioavailability from the topically applied drug product.
- the amount of drug substance in the SC over a certain time period is directly proportional to the amount reaching site of action.

Available data in humans indicate that these assumptions have not been verified and in some cases are contradicted.

2. The current proposal also does not address the following questions raised by **Dr. Jonathan Wilkin,** Director, Division of Dermatological and Dental Products (DDDP) at the 10/23/98 Adv, Comm. Mtg. in which he challenged the assumptions upon which DPK is based. *"the key question . .is the DPK* AUC of topical dosage *forms* analogous fo *the* plasma *AUC* of oral *dosage* forms? I call this the *grand* analogy. *Again, stratum comeum is not the same thing* as *skin" (Ref 1, page III).* He based these questions on (Ref. 2):

. *"Before DPK method is adopted as a basis for BE, it must be shown that differences in DPK capture or reflect* significant clinical/y *important differences* in formulation" Shah et al. Pharm. Res. 1998 15:167-171.

- *"The skin stripping technique thus is subject to the criticism that in many cases, the drug concentration at fhe site of action is not measured and may not correlate with the BA and BE of* topical dosage *forms",* Shah et al, Int'l J. Pharm. 1992:82: page 21-28.
- DPK cannot predict drugs delivered via the follicular route. *"DPK is only going to look at the stratum comeum, but in fact the vehicle and active can go through the stratum corneum or it can go through the follicle".* (Ref 1, page 113).
  'Although the qualitative *evidence for the "shunt" pathway is strong, there is* a *need for* a *well-characterizedpharmacokinetic model for quantifying the relative contributions of each route"* H. Schaeffer et al, in Prediction of Percutaneous Penetration, edited by Scott, R.C. et al IBC Technical Service
- .Healthy vs. diseased skin: *"When a dermatological drug is used, it is usually applied to diseased skin, which may not have the same permeability as healthy skin (e.g., in psoriasis or eczema). To simulate diseased skin, the stratum corneum can be removed or damaged by chemical or* mechanical trauma." (from Jamoulle and Schaefer) Cutaneous Bioavailability, Bioequivalence and Percutaneous Absorption, In Vivo Problems and Pitfalls. In Topical Druo Bioavailabilitv,

Bioequivalence and Penetration edited by V.P. Shah and H.I. Maibach, Plenum Press, NY 1993; Chapter 7:129-153.

- The contribution of excipients to safety and efficacy. *'The problem is* that *the only consideration is whether different ingredients affect the safety of proposed drug product There is no consideration of changes in: "vehicle effects" that could* effect efficacy. " (Dr. J. Wilkin, Ref 2).

- *'If one can assume* that *DPK* as a *technique* can *become reproducible, both within and among laboratories, then one can assume that DPK at least has the potential to become a CONTROLLED ARTIFACT. The next consideration is the scientific and regulatory utility of DPK as a controlled* artifact". (Dr. J. Wilkin, Ref 2).

3. Validation of methodoloav. A presentation on the validation of the DPK was made by the FDA (S. Shrivastava) that covered all the information required to validate the DPK procedure. But as stated by **Dr. McGuire** (chairman, DODAC) *"The very best data I saw today was Dr. Shrivastava's and that was, in fact, idealized data. Those were not* real *observations. I wished there had been data derived from laboratory investigations".* (Ref 1,).

Data presented in the recent FDA proposal demonstrates the failure to validate DPK as reproducible by a given investigator for the same drug product.

4. Does not address the concerns raised by several members of the FDA Joint Advisory Committee on 10123198.

- **Dr. DiGiovanna**: *"What I called it* was *pharmacologic stratum corneum kinetics that did not relate to skin but* stratum *corneum* (Ref I; page 259).
- **McGuire:** *"I think to confuse the issue of uptake and pseudosfeady state and elimination from stratum corneum with something that is happening in diseased skin, I think that is yet to be shown, and I don't think you showed it today* (Ref 1, page 263).
- **Dr. Mindel:** *"As a minimum requirement a technique be validated by two peer reviewed published articles showing that the class of drug* has *mef the standards for the test showing that it is a valid test method.. . . . .*
- **Dr. Kilpatrick** *commenting on L. Pershing's presentations: " I agree with Dr. Lavin.. ..how easily it is to design* a *study which shows your most commonly repeated phrase, not statistically different. Sample sizes were low and . . .you can't real/y conclude anything* (Ref 1, page 21 I)."

5. Does not address the major scientific concerns of members of AAPS and PhRMA as listed below and discussed in more detail in the attached document.
   - Correlation of DPK and clinical safety and efficacy must be demonstrated for each particular class of compounds, each formulation and each indication.
   - Proper validation of the DPK methodology is still outstanding
   - Oct 23 presentation by Dr. Shah on Q1 (qualitative) and Q2 (quantitative) composition and test and reference confirmed (see page 21 of transcript) *"the product contains near/y qualitative/y the same ingredients and quantitatively almost the same types of composition".*
     - As the Interim Inactive Ingredient Policy was revoked on 4/30/99 (FR DOC 99-10798), PhRMA strongly proposes that the Guidance states specifically that Q1 be identical and Q2 be ± 5%.
     - Changes in Q1 and/ or Q2 for Innovators products may require additional safety studies, i.e. photobiology and photocarcinogenicity, that are not addressed in the current Guidance.
   - Statistical metrics need to take into account very high inter and intra variability with respect to subject, site, and investigator variability,

PHRMA strongly recommends that the present guidance should not move forward until data are available validating DPK as a surrogate marker of clinical efficacy and safety of topical skin products.

References:

1. Proceedings of Joint Meeting of the Advisory Committee For pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee, October 23, 1998.

2. Dr. Jonathan Wilkin, FDA, presentation during Joint Meeting of the Advisory Committee For pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee, October 23, 1998.

PhRMA TOPICAL DRUG PRODUCT TASK FORCE REPORT
ON FDA PROPOSED REVISED DRAFT GUIDANCE
MADE AVAILABLE ON MAY 24, 1999 FOR EXPERT PANEL REVIEW

AUGUST 24, 1999

I. Purpose

The purpose of the proposed FDA document (5/24/99) is to present currently available information to the Expert Panel about the proposed DPK procedure in order to allow further consideration of this approach. The goal is to permit the Biopharmaceutics Coordinating Committee of the FDA to finalize the June 1998 draft guidance.

The present proposal by FDA has ignored important issues regarding DPK raised earlier by both Dr. Roger Williams and Dr. Jonathan Wilkin (FDA), PhRMA and as well as members of DODAC / ACPS) during an Advisory Committee Meeting (October 1998).

No data are presented in the draft document, which validate DPK as a surrogate for clinical efficacy and safety of topical skin products.

Conflicting results are provided in three (D. Caron et al. J. Am. Acad. Dermatology: 23, 458-462, 1990, L.K. Pershing et al. Int. J. of Pharmaceutics, 86, 201-210, 1992, and H-J Weigmann et al. Skin Pharmacology In Press) out of five studies. It is questionable whether these studies establish correlation between DPK and skin blanching for corticosteroid products. In the two other studies, no correlation between DPK and skin blanching was obtained (L.K. Pershing et al. Arch. Dermatology 130:740-747, 1994 and L.K. Pershing et al. Under preparation). **Thus, we question whether a method that does not correlate with an accepted BE method (skin blanching) can be considered a valid surrogate. Validation of one surrogate against another unvalidated surrogate, instead of clinical outcome, is questionable.**

Two examples of DPK data presented at the ACPS/DODAC meeting on October 23, 1998 are included in present proposal. The first example (Dr. Pershing, section VI. 1 of proposed document) shows **no** correlation between DPK and clinical efficacy for a miconizole nitrate vaginal cream product. PhRMA has great concern regarding use of DPK as a surrogate measure for a topical vaginal product. Since there is no stratum comeum in the vagina, there is no rational basis for SC concentration in skin to be correlated to vaginal mucosal concentration. Please note the DODAC raised similar concerns on this issue during the advisory committee meeting on Oct. 23, 1998. **The scope of this Guidance must be limited to skin tissue only.**

The second example (P. Lehman's presentation, section VI.2 of proposed document) the authors claim a correlation between DPK and TEWL/desquamation for tretinoin

products. Despite the fact that a dose-response has been shown for TEWL values vs. RETIN-A concentration, TEWL and desquamation have yet to be accepted as surrogates for tretinoin product bioequivalence. In fact, the FDA's review of the Penederm NDA Summary Basis of Approval shows that RETIN-A gel and Penederm gel had identical TEWL but were not bioequivalent in clinical studies. This example indicates the inability of TEWL measurement to predict clinical outcomes, and illustrates the inappropriateness of validating one surrogate against another unvalidated surrogate.

The proposed document also includes summary of DPK studies available to FDA. However, **no** data on validation of skin stripping or results of a pilot study are provided. The Appendix C in the document states what should be included in such validation but provides no data. The proposal does not discuss whether variability of multiple origins (inter- and intra-site, inter- and intra-subject, inter- and intra-investigator, etc.) is so large and unmanageable as to call entire method into question.

Reproducibility of DPK results has not been shown within and between laboratories and investigators. The proposed document shows a study of DPK available to FDA in section IV. The product "XYZ" was tested by investigator ABC in two separate studies, "1" and "3". In Study 1, investigator ABC found the test and reference product to be bioequivalent (AUC C.I. = 89.1 -105.0). In Study 3, test and reference product were NOT bioequivalent (AUC C:I. = **76.2 – 84.7). This demonstrates difficulty to validate the reproducibility of DPK.**

The relative sensitivity of DPK vs. clinical or pharmacodynamic measures is not the issue; it is whether DPK response can be a reliable surrogate for clinical safety and efficacy.. **It is the consistency of DPK to predict the clinical outcome, not only the sensitivity of the method that needs to be demonstrated.**

Finally, the FDA-proposed document recommends DPK as a surrogate for BE when test and reference product are qualitatively (Q1) same and/or functionally similar and should be quantitatively (Q2) similar to ±10% (citing the SUPAC-SS approach). PhRMA objects to this final recommendation, since:

- DPK has yet to demonstrate correlation to clinical efficacy and safety.
- As the clinical efficacy and safety of topical skin products is a composite of drug and vehicle (excipients) the test and reference product must be qualitatively identical (Q1) and quantitatively (Q2) similar (± 5%).

The SUPAC proposal addresses post-approval changes, while BABE for an ANDA product is a preapproval requirement. The premise behind SUPAC is to reduce regulatory burden for product for which a significant body of information has been established. The comparison of "Test" and "Reference" products manufactured by

different firms, at different sites by different processes can in no way be consistent with SUPAC.

Changes in Q1 and/or Q2 for innovator products may require additional safety studies, i.e. phototoxicity and photocarcinogenicity, that are not addressed in the current guideline.

PhRMA strongly recommends that **identical** (not merely functionally similar) excipients be required for generic products. Any deviation may affect safety and should be forwarded to the new drug review division of FDA, who may require the product be reviewed as an NDA.

PhRMA strongly recommends that the guidance should not move forward until data are available validating DPK as a surrogate marker of clinical efficacy and safety of topical skin products.

The issues with DPK and validation are given below:

Summary of DPK Issues

- **Correlation between DPK and clinical safety and efficacy must be demonstrated for each particular class of compounds, each formulation and each indication.**

- There are inadequate DPK data correlating SC drug concentrations to concentrations at the target tissue (epidermis/dermis/hair follicle) or in systemic circulation.

- There are clear data demonstrating that DPK may fail to predict safety and efficacy for drug products that are delivered to and through hair follicles.

- The DPK model does not assess the known vehicle impact on safety and efficacy, therefore, the test product must meet qualitative and quantitative (<±5.0%) requirements.

- **Single dose DPK studies on the healthy adult arm will not** consistently predict equivalence in:
    - diseased skin
    - geriatric and pediatric age groups
    - multiple dose conditions
    - skin with permeation characteristics different from the arm.

- The current guidelines do not address whether these assumptions hold true for combination products, especially when the active ingredients have different targets.

- DPK is inappropriate for vaginal, nail, transdermal, and mucosal products.

Validation Issues

- **Data are lacking that validate the proposed DPK method as a reliable, precise and accurate predictor of clinical safety and efficacy, and therefore the BA/BE for topical drugs.**

- Skin stripping is not well controlled. There is large **intrasubject variability even from adjacent sites, as well as large intersubject variability.**

- The amount of SC removed (recovered) is unknown for each site. In addition, there is a concentration gradient across the SC. Unlike plasma, the SC is non-homogeneous in nature. Therefore, it is inappropriate to normalize drug concentration per gram of SC . As a standard area is stripped, use of cm^2 is also not appropriate.

- The inability to normalize the data means no meaningful information regarding the rate and extent of absorption of reference and test drug can be obtained.

- **Mass balance** (unabsorbed drug, drug in the SC, drug in epidermis and dermis, and well as systemically absorbed drug) needs to be studied in order to ascertain that DPK is valid and not simply reflective of drug in residual formulation on the skin surface.

- The proposed 10 strip samples only represent a small portion of the SC, and the amount of SC collected is highly variable from person- to- person and site-to-site. **It is unknown whether the amount of drug in these ten strips is in the SC furrows or represents absorbed drug.**

- TEWL studies show that there is a significant barrier function retained until much deeper layers in the SC are removed (greater than 25 strips for skin type II/III and more than 60 strips for skin type VM). (Van Der Valk and Maibach, Clin. and Exp. Derm. 15: 180, 1990; Reed, Ghadially, and Elias, Arch. Dermatol. 13 1: 1134, 1995) This brings into question whether the proposed protocol accurately reflects the drug levels in the SC, let alone delivery to the epidermis and dermis.

- To reach the deeper levels, at least 30 strips must be removed. This can lead to pain, scarring, and hyperpigmentation.

II. Conceptual approach

The conceptual approach ignores the importance of appendageal transport (sebaceous glands, hair follicle), recommending DPK studies in healthy subjects. This ignores differences in stratum comeum and skin anatomy/physiology/metabolism of healthy

versus diseased skin. Therefore the recommended surrogate may not consistently predict equivalency.

The conceptual approach recommends requirement of BA studies during IND/NDA but BE studies for ANDA's and post approval changes are sufficient for equivalency. We feel that for the T and R to be equivalent they should be shown to have equivalent systemic bioavailability (BA) as well as being bioequivalent (BE).

As stated in the proposed document by FDA, the conceptual DPK approach is based on the **hypothesis** and **assumptions** given below:

- Two products exhibiting similar exposure patterns in the intact stratum comeum (SC) will deliver the drug at the same rate and extent to the site(s) of action in patient with dermatological disorders.

- Appearance and disappearance of active drug substance in the stratum comeum will adequately reflect bioavailablity from the topically applied drug product, irrespective of the site of action.

- The amount of drug substance in the SC over a certain time period is directly proportional to the amount reaching the site of action,

Available data in humans indicate that these assumptions have not been verified and in some cases are contradicted.

Analogies between DPK procedure and systemic exposure measure (blood/plasma concentration profile) for orally administered drug are made, with which we do not agree. This point has been well argued during advisory committee meetings by FDA-reviewing division director, Dr. Jonathan Wilkin.

The discussion centers on the appropriateness of DPK as a BE measure, since it assesses availability of drug to the site of action by determining SC concentration over time. However, the site of action of most topical drugs is not precisely known, so relevance of DPK to BA at the "site of action" is unclear. BE should be measured by a procedure which is known to reflect delivery of drug and active metabolites to the site of action. DPK has not been shown to be representative of target site concentrations and does not address metabolites at all. Release of drug from vehicle matrix, transit through SC, and metabolism and permeation through living skin, may all play a part in the delivery of active moieties to the site of action. Looking only at SC concentrations (DPK) may not predict PD or clinical activity. Differences in permeation among body sites and skin condition (scaliness, erythema, etc.) are also not addressed.

The reference of *in-vitro* release test (IVRT), cited in SUPAC-SS, as surrogate test to product quality, is proposed in the present document as a test to signal bioINequivalence.

The currently proposed document ignores the limitations of IVRT described in SUPAC-SS, which are:

- *in-vitro* release testing, alone, is not a surrogate test for *in vivo* BA or BE
- *in-vitro* test is not required as a routine batch-to-batch quality control test
- *in-vitro* release rate should not be used for comparing different formulations across manufacturers.

The limitation of IVRT to detect significant changes in composition and process for a water soluble drug in cream products has been published recently (Kril, Parab et al. Pharmaceutical Technology, page 164, March 1999).

The key question the conceptual approach raises is whether DPK is sensitive to detect formulation changes such as components and composition and method of manufacturing. Thus DPK has yet to prove its assumption that it can capture or reflect significant clinical important differences in formulation.

III. Validation of the DPK Approach

The issues that need to be considered for validation are described in Appendix C of proposed document. However, no data are provided to demonstrate a suitable protocol or to evaluate the outcome. DPK should not be accepted until there is validation not only of the precise procedure that should be employed, but a demonstration that the DPK method is a reliable, precise and accurate predictor of clinical safety and efficacy, and therefore can predict BABE for topical drugs.

Correlation between DPK and clinical safety and efficacy must be demonstrated for each particular class of compounds, each formulation and each indication.

One issue not discussed is whether variability from multiple sources (excess drug removal, skin site variability, inter- and intra-subject variability, intra and inter-investigators, etc.) is so large and unmanageable as to call the entire method into question.

Validations need to be done before the draft guidance is finalized and not afterward. As no data are provided to the expert panel to assure that validation issues outlined in Appendix C and clinical relevance of DPK are addressed, we recommend that the guidance should not move forward until validation is complete.

IV. Literature reports

Several literature reports are provided containing information on different aspects of DPK. We have reviewed these reports and we conclude that there are several key issues

on DPK which are not yet fully addressed. Our summary of review of each literature report is given below.

Literature Report 1

The proposed document refers to "Workshop report: Pharm. Res. 15: 167-l 71, 1998" with conclusion that the DPK method is a potentially suitable method to document bioequivalence of topical dermatological dosage forms.

Although the above conclusion was drawn at AAPS/FDA workshop in 1996, the workshon also identified that DPK method assumes:

- the excipients are pharmacologically inactive,
- the stratum comeum concentration-time curves are directly related to the concentration-time curves of the active drug in the epidermis and the dermis,
- that the differences in DPK captures or reflects significant clinically important differences in formulation.

Available data in humans indicate that these assumptions have not been verified and in some cases are contradicted.

A similar AAPS/FA Workshop held in 1990 included the following statement in its report: "The skin stripping technique thus is subject to the criticism that, in many cases, the drug concentration at the site of action is not measured and may not correlate with BA and BE of topical dosage forms." Shah et al, Int'l J. Pharm (82):21-28 (1992).

Dr. J. Wilkin (FDA) described DPK as a **"Controlled Artifact"** during the 10/28/98 Advisory Meeting.

Literature Report 2.1

Scientific report in Skin Barrier, ed. by H. Schaefer and T.E. Redelmeier, pp. 147-150, 1996 is included in the document as evidence to show that tape stripping'with a suitable analytical method yields an acceptable DPK approach to measure BA.

The authors cautions the importance of "the removal of free residual formulation at the end of penetration period and before stripping, is particularly important and care should be taken to ensure choice of medium (mild detergent or solvent) does not cause Tubsequent redistribution in the layer underneath the surface. second tape strip should be discarded "because they contain superficial formulation vehicles."

Neither Appendix C of the proposed document nor the references show any data to validate that the procedure adopted to remove free residual formulation (wiping with

cotton swab or Q tips, washing area with mild soap) ensures complete removal of free unpenetrated residual formulation and does not redistribute drug underneath the surface (deep SC, epidermis/dermis).

According to Dr. Franz (Advisory Committee Meeting, October 1998) – the first ten strips of SC contains free unpenetrated drug formulation, so discarding just first two strips as recommended by FDA may not be adequate.

Dr. Schaeffer cites in Fig. 47 that:

There is concentration gradient across SC

Considerable (four-fold) inter-individual variability in the material recovered in the strips

Data should be expressed as amount of drug/mg of harvested SC

Yield of SC removed may be influenced by length of contact time and composition of some formulations, thus it is likely that the yield of SC will vary for different protocols as well as laboratories.

As there is a concentration gradient in SC, we recommend comparing statistically the concentration gradient in SC between test drug and RLD at each time point to determine equivalency.

In Fig. 47C the reference shows that ten strips contribute to only 35% of SC. Thus the material removed will not represent 100% of the drug distribution in SC.

Dr. Schaefer shows data in Figure 48 from Rougier et al. (Literature Report 3.1) and states that tape stripping can be used to predict the percutaneous absorption of compounds after a relatively short-term application. This data was generated in hairless rats, whose skin is very leaky, with idealized solution formulations, hence the relevance of this data to humans is questionable. The author cites Pershing et al. (Literature Report 6) for SC concentration use in bioequivalence. (Please see additional comments on Literature Report 6)

The most important conclusion of this Literature Report 6 (page 149) is:

"Though it (skin stripping) has found extensive use in several laboratories, it cannot yet claim to be validated in a wide variety of laboratories."

Thus, only the Rougier data and no other data is used to refer to validity of skin stripping for BA. No new references are cited, so we agree with the conclusions of the paper. (First validate the DPK concept and then finalize the guidance and not vice-versa.)

Literature Report 2.2

J.C. Jamoulle and H. Schaefer, "Cutaneous bioavailability, bioequivalence and percutaneous absorption. In vivo methods, problem and pitfalls" In: Topical Drug Bioavailability, Bioeauivalence. And Penetration, ed. by V.P. Shah and H.I. Maibach. pp. 129-153, 1993.

The above reference is cited in the document as evidence that the tape stripping technique (DPK) is correlated to systemic bioavailability. Again the Rougier reference (Rougier A et. al. J. Invest Dermatology. 81:275-278, 1983) is the only one cited to show a relationship between SC concentration and BA.

The following quotations form Jamoulle and Schaefer show the limitations of skin stripping (DPK).

Page 140 – "Although this technique (tape stripping) is of interest, to our knowledge it has not yet been accepted or recommended by the regulatory agencies in bioequivalence determination, possibly because of its apparent limitations in the area of very lipophilic drugs (e.g. retinoids or antifungals such as ketaconazole), where the quantity measure is too low."

Thus, instead of supporting the DPK method, this reference emphasizes the limitations of skin stripping to determine BA.

Page 137 – "It has been shown that an "inactive" ingredient of the formulation can have effect on skin metabolism."

Excipients in topical products are not inert, they can impact the pharmacological activity of the active ingredient in several ways. They can impact on permeability, metabolism, clearance, (i.e. pharmacokinetics) of the drug. Therefore Q1 and Q2 must be equivalent for test and reference.

Page 141 - "The metabolic activity and permeability of skin may be changed under the effect of repeated exposure to the product during toxicity or clinical study. The metabolic activity and permeability may be increased by irritation or decreased due to the healing of the disease process. The treatment effect may increase the thickness of stratum comeum, the reservoir effect or penetration. Because this effect cannot be assessed by annlication of single dose of the test compound. it must be studied during repeated application."

These observations by Dr. Schaeffer have been confirmed by Dr. Pershing in her work with 2% topical ketoconazole in tinea pedis presented at the Jnt. Adv. Committee Mtg. In this work there was a clear difference in SC concentrations between diseased and healthy feet, as well as between single and multiple doses. It should also be noted that

forearms concentrations in this study did not have the same kinetics as either the healthy or diseased skin.

These data clearly show that SC concentrations from normal forearm skin can not be extrapolated to diseased skin, or other skin sites, even with a compound whose site of action is the SC.

BABE studies with multiple application emphasized.

Page 137 (Figure 5): "Factors such as number of follicles can influence the drug delivery into the skin."

Therefore, skin stripping (SC concentration) cannot predict concentration in hair follicle emphasized.

Page 137: "When a dermatological drug is used, it is usually applied to diseased skin, which may not have the same permeability as healthy skin (e.g. in psoriasis or eczema). To stimulate diseased skin, the stratum comeum can be removed or damaged by chemical or mechanical trauma (stripping)."

Page 139 (Figure 6a) of this reference shows concentration time profile of drug in diseased skin is entirely different from that of normal skin.

As SC is damaged is absent or diseased conditions , the usefulness of measurement of drug concentration in SC from normal skin is highly questionable.

Page 146 - "In general, it can be stated that bioequivalence can be claimed for two formulations of the same product if they show the same local and systemic bioavailability of the active moiety."

Here Dr. Schaefer emphasizes the need for determining skin as well as systemic blood concentration time profile for BABE

Literature Report 3. 1

A. Rougier and C. Lotte, "Predictive approaches: I. Stripping technique" In Topical Drug Bioavailability, Bioequivalence And Penetration, ed. By V.P. Shah and H.I. Maibach, pp. 163-181, 1993.

This reference is sited by the FDA as a evidence to show that the drug concentration reflects total drug absorption, hence DPK can be used to predict BA. However, a review of this reference raises following concerns.

- The data on influence of dose, vehicle, and application time is generated in hairless rats, which have been shown to have leaky skin (Lauer, Elder and Weiner. J. Pharm. Science, 86:13-17 1997). Solution formulation containing penetration enhancers, such as, ethanol, Triton X-100, ethylene glycol in water, and highly permeable drugs, such as benzoic acid, acetyl salicylic acid, nicotine, and salicylic acid, were used in this study to create ideal conditions. The relevance of these animal studies using highly permeable drugs in solution formulation to humans is questionable.

- The study in human subjects was also done with a highly permeable compound (benzoic acid) in a solution formulation of ethylene glycol +10% Triton X-100. Application of this single study in humans, to all topical drugs (including highly lipophilic compounds) in different topical dosage forms is questionable.

- Page 168 (Table 1): Shows that for highly lipophilic compounds, such as testosterone, dexamethasone, dehydroepiandrosterone, and some water soluble compounds (sodium lauryl sulphate and theophylline) there is a poor correlation between the amount in the skin strips and amount excreted into the urine.

- The limitations of using skin stripping to assess bioavailability are: difficulty in assessing rate of penetration and inability to estimate metabolism.

- We agree with conclusion of Rougier et al (Arch Dermatology Res 278: 465-469, 1986) that "examination of other molecules of varying physiochemical properties and additional anatomic sites, should be examined before overgeneralizations are made."

Literature Report 3.2

H.I. Maibach and R. J. Feldman, Effect of applied concentration on percutaneous absorption in man, J. of Invest Derrn 52:382, 1969.

The above abstract is cited by FDA in this proposed document as evidence to show correlation between DPK and drug absorption. However, this reference does not present any data on stratum comeum concentration (DPK) to draw above conclusion. The authors have observed that by increasing the concentration of applied drug/cm^2 always increases total absorption of drug. The authors conclude that grams amount of some compounds can be absorbed through normal skin under possible conditions of therapeutic and environmental exposure.

What we conclude from this reference is that there can be large systemic exposure of drug. Thus evaluation of systemic exposure is very important and that test drug should have similar systemic exposure as reference listed drug to be bioequivalent and this is important for safety.

Literature Report 4

The document refers to (D. Caron et al. J. Am. Acad. Dermatology; 23-462, 1990) as an evidence to show correlation between DPK and vasoconstriction (skin blanching).

In this paper, Caron et. al. have evaluated stratum comeum concentrations (pharmacokinetics) and skin blanching (PD) in human subjects (n=12) for 2.5% hydrocortisone creams. HYTONE cream and SYNACORT cream having different qualitative compositions were used. The product (dose = 44 and 8 mg/cm^2 for skin blanching and skin stripping, respectively) was applied under occlusion. At 4, 6, 8, 16, 20 and 24 hours postapplication, the occlusive cover was removed and the area was wiped clean of excess formulation. One hour after removal, skin blanching measurement and skin stripping was performed.

We have the following concerns with the above reference:

The PD (skin blanching) and PK (skin stripping) studies were done after applying 44 and 8 mg/cm^2 respectively of product under occlusion. The PD and PK data obtained is questionable, because under clinical conditions the dose is 2-3 mg/cm^2 and not under occlusion.

There is no correlation between SC concentrations and skin blanching. For example, the SC concentrations for HYTONE increase from 3.3 to 3.8 $\mu g/cm^2$ from 16 to 24 hours (Fig. 2) where as the skin blanching decreases from 1.16 to 0.7 (Fig. 4).

It can be noted that at 24 hours there is significant difference in stratum comeum concentration between two formulations where as the skin blanching is similar. This is shown in Table 1.

Table 1: Comparison of skin blanching and stratum corneum concentration at 24 hours.

	SC Concentration (mg/cm^2)	Skin Blanching
HYTONE	4.0	0.72
SYNACORT	1.4	0.68

Therefore, we feel there is no direct correlation between SC concentration and skin blanching in this reference.

Literature Report 5

Inter- and intra-subject variability: L.K. Pershing, L.D. Lambert, V.P. Shah and S.Y. Lam. Int. J. of Pharmaceutics, 86, 201-210, 1992.

The above scientific reference is included in the proposed document to show inter- and intra-subject variability and similarity between (correlation) results of tape stripping (DPK), visual blanching and chromometer reading for betamethasone dipropionate products.

In this study (Figure 2B), DIPROSONE lotion (DSL) and DIPROLENE augmented ointment (DLO) gave similar SC concentrations. However, the literature (Fitzpatrick et al, Dermatology in General Medicine, 4th Edition, McGraw-Hill, New York, NY, 1993) suggests that DSL is a Category 5 corticosteroid, whereas DLO is a Category 1 in its clinical potency. Thus, there is no correlation between clinical efficacy and SC concentrations.

In addition, from Figure 2 of this reference we observe rank order of:

Visual blanching DLO>DSL>DLC>DSC≥DSO
SC Content DSL>DLO>DSC>DSO≥DLC

We do not see similar rank order between visual blanching and SC content for these five products as claimed by FDA. The correlation between SC concentration and visual blanching was R=0.6 and was not statistically significant.

Another deficiency of the procedure is use of tape strips no. 2-l 1 for calculating SC concentrations. Generally, the systemic absorption of corticosteroids is minimal (<5%). **Thus the huge amount of drug observed in the tape strips (38-92% of applied dose) in this study, raises the question of whether the amount of drug in the SC represents residual drug on the skin surface or in skin furrows, rather than drug penetrated in the SC.**

As noted in other studies, there is a large amount of inter and intra-subject variability in the SC content (Table 2).

Table 2. Intra and Inter-subject Variability in Literature Ref 5.

	N	Intra-subject	Inter-subject
SC Content variability	3	8-47%	77-99%
Visual blanching variability	10	0-28%	36-76%

As the suggested bioequivalence test is paired comparison, intra-subject variability will be useful to calculate sample size. However, only three subjects have been used to determine intra-subject variability, this sample size is too small to represent the population. Hence the data provided in the reference is not useful.

Literature Report 6

"Topical 0.05% betamethasone dipropionate, pharmacokinetic and pharmacodynamic dose-response studies in humans, L.K. Pershing, C. Lambert, E.D. Wright, V.P. Shah, R.L. Williams. Arch. Dermatology: 130: 740-747, 1994.

This example is cited in the document as an example of "drug uptake and elimination of betamethasone dipropionate, DPK and pharmacodynamic dose-response studies in humans." However, review of the article shows that:

No correlation was found between SC concentration, (DPK) and skin blanching (PD), for dose response, such as dose duration, varying concentration and film thickness.

Authors conclude that quantification of drug uptake, retention and elimination from the SC alone may be insufficient to account for an observe clinical response.

In conclusion there is no correlation between SC concentration (DPK) and skin blanching (pharmacodynamics).

The SC concentration (uptake and elimination), shown by FDA in a recent proposal, is not shown in this Literature Report. . How can one have two different drug concentrations at 6 hours, one for drug uptake (0.08 mcg/sq. cm) and another for drug elimination (0.13 mcg/sq. cm)? The CV% ranges from 23-92%. A noted in other studies, there is a large amount of variability.

Literature Report 7

Dose proportionality studies: L.K. Pershing, S. Bakhtian, C.E. Pricelet, J.L. Corlett and V.P. Shah. Under preparation.

This report gives examples dose proproportonality of triamcinolone acetonide cream and betamethasone dipropionate cream using the stratum comeum concentration at 6 hours after application .

The data for betamethasone diproprionate is from Literature report 6 (Pershing et al Arch. Dermatology: 130: 740-747, 1994) which we have discussed on previous page.

The details of study design for triamcinolone acetonide cream DPK, and PD study are not provided, however, the coefficient of variation skin stripping dose ranging study is 59-175%.

The conclusion drawn by FDA is that "DPK can differentiate between different strengths of topical dermatological drug products, where as pharmacodynamic end point do not." This statement implies to us that there is no correlation between DPK and pharmacodynamic end point thus suggesting that DPK is not a surrogate for pharmacodynamic end point skin blanching.

Literature Report 8

DPK, pharmacodynamics and clinical outcomes. H-J. Weigrnann, et al, Skin Pharmacology. In press.

Three clobetasol propionate cream products, reference cream (TEMOVATE, Glaxo), generic cream (approved product) and reference emollient cream (TEMOVATE E, Glaxo), were investigated in 6 subjects for DPK. The skin blanching, PD-study was also done (no data on PD is provided in the document by FDA). The authors claim similarity in DPK and PD for TEMOVATE cream and generic cream but not for TEMOVATE E cream. FDA in this document claim labeling for R cream and R emollient cream is different, suggesting R emollient cream is less potent than R cream.

In this document FDA concludes following with this example, "1) DPK measures and biological response in terms of PD is correlated 2) DPK can detect formulation differences (Appendix D, Figure 1) and 3) DPK can serve as a surrogate for clinical efficacy and blanching."

FDA has not provided us with the PD data to confirm correlation between DPK and PD. **Review of the published article suggests that the PD determination in this study was by nonstandardized observation. We disagree with conclusions 2 and 3, and statement by FDA that labeling of R cream and R emollient cream is different, thus, suggesting R emollient cream is less potent than TEMOVATE cream.**

According to Glaxo-Wellcome, there is no evidence to support a statement that TEMOVATE emollient cream is less potent than TEMOVATE cream.

- Both TEMOVATE cream and TEMOVATE emollient cream are designated as "super-high potency corticosteroid" formulations in their labels.

- Because of their potential to suppress the HPA axis, both TEMOVATE cream and TEMOVATE emollient cream labels, state that "treatment beyond 2 consecutive weeks is not recommended" and the "total dose should not exceed 50 g/week."

- TEMOVATE emollient cream and TEMOVATE cream were compared by Glaxo-Wellcome in a vasoconstrictor study with 30 volunteers. There was no difference between the vasoconstrictor potency of these two creams.

- The TEMOVATE emollient cream label includes treatment "for up to 4 consecutive weeks" but, is limited to "5% to 10% of the body surface area." It is important to note that the extension from 2 to 4 weeks includes a restriction on the body surface area for TEMOVATE emollient cream. This 4 week treatment label was a Phase IV investment by Glaxo-Wellcome to give a commercial advantage (i.e. differentiation) of TEMOVATE emollient cream over generic clobetasol cream. For these reasons, the 4 week label is not an indication that TEMOVATE emollient cream is less potent than TEMOVATE cream.

- While TEMOVATE cream and TEMOVATE emollient cream have not been compared in a clinical trial, the efficacy results of each cream from individual trials were comparable.

The study cited by FDA in this document, has been published recently (J. Weigmann et al, Skin Pharmcol Appl Skin Physiol. 1999; 12:46-53.) In this unblinded study, SC concentrations were evaluated in only six subject with an application dose of 5.5 mg/cm2 and SC concentrations, determined at 0.5, 2, and 6 hr postdose. It is surprising to note 69 and 54 % of the applied dose in strips 2-11 for TEMOVATE cream and clobetasol proprionate (USP) cream, respectively. This questions whether the amount in the SC represents absorbed drug or drug remaining on the skin surface and/or furrows and whether the swabbing the skin and discarding the first strip is an effective means of removing the unabsorbed drug. We feel it does not. What this study shows is the spreadability characteristic of each product, i.e. TEMOVATE cream has similar spreadability as clobetasol propionate (USP) cream, where a TEMOVATE E cream has greater spreadability.

As the cleaning procedure was not validated, we question the results of this small study. In addition, the only PD determination in this study was by nonstandardized observation.

I. Summary of DPK Studies Available to FDA

The proposed document also includes summary of DPK studies available to FDA. However, **no** data on validation of skin stripping or results of a pilot study are provided.

Reproducibility of DPK results has not been shown within and between laboratories and investigators. The product "XYZ" was tested by investigator ABC in two separate studies, "1" and "3". In Study 1, investigator ABC found the test and reference product to be bioequivalent (AUC C.I. = 89.1 -105.0). In Study 3, test and reference product were NOT bioequivalent (AUC C.I. = **76.2 – 84.7). This demonstrates that it is difficult to validate the reproducibility of DPK.**

VI DPK data presented at ACPS/DODAC meeting on October 23, 1998

Two examples of DPK data presented at the ACPS/DODAC meeting on October 23, 1998 are included in present proposal. The first example (Dr. Pershing, section VI. 1 of proposed document) shows **no** correlation between DPK and clinical efficacy for a miconizole nitrate vaginal cream product. PhRMA has great concern regarding use of DPK as a surrogate measure for a topical vaginal product. Since there is no stratum comeum in the vagina, there is no rational basis for SC concentration in skin to be correlated to vaginal mucosal concentration. Please note the DODAC raised similar concerns on this issue during the advisory committee meeting on Oct. 23, 1998. **The scope of this Guidance must be limited to skin tissue only.**

The second example (P. Lehman's presentation, section VI.2 of proposed document) the authors claim a correlation between DPK and TEWL/desquamation for tretinoin products. Despite the fact that a dose-response has been shown for TEWL values vs. RETIN-A concentration, TEWL and desquamation have yet to be accepted as surrogates for tretinoin product bioequivalence. In fact, the FDA's review of the Penederm NDA Summary Basis of Approval shows that RETIN-A gel and Penederm gel had identical TEWL but were not bioequivalent in clinical studies. This example indicates the inability of TEWL measurement to predict clinical outcomes, and illustrates the inappropriateness of validating one surrogate against another unvalidated surrogate.

II. Unpublished DPK Information on Tretinoin.

Response is in Executive summary and Purpose section of this PhRMA document.

III. Further Research

Scientific proposal should consider:

- Therapeutic class with different targets in skin.
- Same drug with different delivery systems.
- Blinded three-arm comparison, RLD, Test drug bioequivalent, Test drug non-bioequivalent.
- Product application dose 2 to 3 mg/ CM^2
- Studies should include mass balance and validation.

Proposal I

Studies should be conducted to confirm that Dr. Rougier concepts of SC concentration to BA applies to drugs with varying physicochemical properties (oil soluble, large and small molecules) and diseased VS normal and different body sites.

Proposal II

We propose to conduct study on Penederm's AVITA cream (0.025% and 0.1%) versus RETIN A cream (0.025% and 0.1%). The clinical data shows that AVITA and RETIN A cream at 0.25% are bioequivalent where as at 0.1% are non-bioequivalent.

Outcome: DPK study should correlate to clinical findings and dose proportionality.

Proposal III

The antifungal product should be a skin product and not a vaginal product.

Proposal IV

Manufacturing variable

We recommend no study be conducted on this proposal at this stage until we conform DPK is an appropriate surrogate.

Iv. Recommendations

Finally, the FDA-proposed document recommends DPK as a surrogate for BE when test and reference product are qualitatively (Q1) same and/or functionally similar and should be quantitatively (Q2) similar to ±10% (citing the SUPAC-SS approach). **PhRMA objects to this final recommendation, since:**

- DPK has yet to demonstrate correlation to clinical efficacy and safety.
- As the clinical efficacy and safety of topical skin products is a composite of drug and vehicle (excipients) the test and reference product must be qualitatively identical (Q1) and quantitatively (Q2) similar (± 5%).

The SUPAC proposal addresses post-approval changes, while BABE for an ANDA product is a preapproval requirement. The premise behind SUPAC is to reduce regulatory burden for product for which a significant body of information has been established. The comparison of "Test" and "Reference" products manufactured by

different firms, at different sites by different processes can in no way be consistent with SUPAC.

Changes in Q1 and/or Q2 for innovator products may require additional safety studies, i.e. phototoxicity and photocarcinogenicity, that are not addressed in the current guideline.

PhRMA strongly recommends that **identical** (not merely functionally similar) excipients be required for generic products. Any deviation may affect safety and should be forwarded to the new drug review division of FDA, who may require the product be reviewed as an NDA.

PhRMA strongly recommends that the guidance should not move forward until data are available validating DPK as a surrogate marker of clinical efficacy and safety of topical skin products.

Exhibit 3

September 17, 1999

Janet Woodcock, MD, Director
FDA-CDER
Mail Stop - HFD-001
Building WOC2, Room 6027
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Woodcock:

In light of the upcoming meeting of the Pharmaceutical Science Committee on September 23-24, I am writing to you to express the American Academy of Dermatology's continued concern with the Food and Drug Administration's (FDA) support of a proposal to allow manufacturers to substitute skin tape stripping for pharmacodynamic measurements (PD) or comparative clinical trials. The Academy does not support issuance of the ***Guidance to Industry Topical Dermatological Drug Product NDAs and ANDSs – In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies*** at this time. We do not believe that data currently exist that support the adoption of skin tape stripping as a method of determining the bioavailability and bioequivalence (BA/BE) of a generic drug to a reference listed drug. Although the Academy is supportive of efforts to decrease costs and to streamline the process of drug approval, we cannot support any method that would put our patients at risk of receiving inferior treatment for dermatologic disease.

Since publication of the draft guidance document, the Academy has informed the FDA on several occasions of its reservations with this approach, and our concerns that it is premature for the FDA to consider adoption of this test as a means of establishing bioequivalence. At the most recent joint meeting of the Pharmaceutical Science and Dermatologic and Ophthalmic Drug panels, dermatologists, skin researchers and representatives of the pharmaceutical industry also expressed reservations with the efficacy of tape stripping. Our specific concerns include – that tape stripping does not accurately measure the drug in the stratum corneum; an accurate measurement methodology that could show BA/BE of a drug in the stratum corneum does not support the assumption that the drug would have the same BA/BE properties for drugs intended for the epidermis, dermis or hair follicle; the proposed methodology does not account for the differences between healthy and diseased skin; and concerns about the reproducibility of the technique.

As you know, the surface of the skin is not flat, it has peaks and valleys like a mountain range or, more appropriately, the skin is like bark on a tree. The topography of the skim presents unique challenges to scientists in their attempts to validate skin tape stripping. On October 23, 1998, Dr. Thomas Franz, a dermatologist and expert in measuring how drugs penetrate the skin, provided testimony to a joint meeting of the Derrnatologic and Ophthalmic Drug and Pharmaceutical Science Committees. Dr. Franz compared 1% Hytone to generic 1% cortisone

using the current FDA accepted vasoconstrictor assay as well as a cadaver skin assay. In both instances, Dr. Franz found the drugs to be different. However, when using tape stripping, following the draft guidance requirements, the drugs appeared to be the same. Dr. Franz had this explanation: "The skin is not flat. That's the statement. There are furrows in the skin. And as one tape strips stratum corneum, one gets stratum comeum cells and one also gets unabsorbed drug in skin furrows and those furrows go down quite far. What we are seeing is drug in the furrows. One percent is one percent. They've [generic drugs] got to give the same answer, and they do . . . but after twelve strips, as we get into seventeen and then twenty-two strips, we finally begin to leave the furrows behind, get into the middle portion of the stratum corneum and now we see statistically significant differences between the two products. "[1] Thus, Dr. Franz showed that routine tape stripping tests are comparisons of free drug, not drug incorporated into the skin.

Dr. Franz is not alone in his concerns. Dr. R. van der Molen of the Laboratory for Electron Microscopy, University Hospital Leiden, The Netherlands, published a study of the relevance of skin furrows to skin tape stripping. In his study, Dr. van der Molen investigated the efficacy of tape stripping in removing complete cell layers from the superficial part of the human stratum corneum. A histological section of the skin that was tape-stripped twenty times clearly showed ***nonstripped skin*** in the furrows, indicating incomplete tape stripping. Indeed, after removing forty tape strips the furrows were still present.[2] The FDA's ***Draft Guidancefor Industry*** recommends a total of twelve tape-strips. The first two strips are assumed to contain the unabsorbed drug and are discarded, while the guidance document assumes that the stratum corneum will be removed in the next ten tape strips.[3] Dr. Prakash Parab testified at the October 23, 1998 meeting that "the proposed ten strips only represent a small portion of the stratum corneum. TEWL data shows that there is a barrier inside the stratum corneum. At least 25 strips had to be removed in [skin] Type II and III, sixty strips in Type IV and V. So this brings up the question of [whether] the proposed ten strips accurately reflects stratum corneum concentration. To reach the deeper layer, one has to strip thirty strips and these thirty strips will cause pain, scarring and hyperpigmentation."[4] If skin tape stripping is an imprecise measurement of the amount of drug in the stratum corneum, how can we with any certainty rely on this method to assess the presence of drug in the deeper layers of the skin or in the hair follicle, especially in the absence of ***in vivo*** experiments that directly validate this speculation?

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[1] Franz, T; ***Advisory Committee for Pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee, Joint Meeting;*** Friday; October 23, 1998.

[2] van der Molen, RG; Spies, F; van 't Noordende JM; Boelsma E; Mommaas, AM; Koerten HK; "Tape Stripping of Human Stratum Comeum Yields Cell Layers that Originate from Various Depths Because of Furrows ***in the*** Skin"; ***Arch Dermatol Res;*** 1997 Aug; 289(9): 514-8.

[3] Center for Drug Evaluation and Research; Food and Drug Administration; ***Guidance for Industry Topical Dermatological Drug Product NDAs and ANDAs – In Vivo Bioavaiiability, Bioequivalence, In Vitro Release, and Associated Studies:*** June 1998.

[4] Parab, P; ***Advisory Committee for Pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee, Joint Meeting;*** Friday; October 23, 1998.

It would appear that the draft guidance document fails to give sufficient pause to skin furrows. In addition, several other skin conditions car affect tape stripping. The level of hydration in the skin, cohesion between cells, the body s he amount and type of body hair present on the test site, and other inter-individual difference- can affect the outcome of tape stripping. Skin tape stripping may also be inappropriate for testing vaginal, nail, transdermal, and mucosal products.

The age and health of the individual may also be a factor. Many dermatologists are concerned that as skin tape stripping studies are performed on the healthy skin of an adult arm, the studies may not accurately predict equivalence in skin that is diseased or in geriatric or pediatric age groups. In recent years, there has been a concerted effort to en e that subpopulations are included in clinical research and trials. In the fiscal year 1996 a ropriations bill, Congress included language urging the National Institutes of Health (NIH to ensure that medical treatments applied to children are appropriate to children and have been tested on children. In March 1998, the NIH issued a policy guideline on the inclusion of children as participants in clinical research.[5] Despite the existence of this guideline, the draft guidance document remains silent on the appropriateness of this technique for assessing bioequivalence in drugs that are used predominantly in children.

The draft document also fails to recognize the differences in the stratum corneum of healthy and diseased skin. At the October 23rd meeting. Dr. Shah asserted that "although the exact mechanism of action for some dermatological drugs is unclear, the DPK approach may still be useful as a measure of BE because it has been demonstrated that the stratum comeum functions as reservoir, and stratum corneum concentration is a predictor of the amount of drug absorbed. "[6] Dermatologists know that the stratum corneum of diseased skin is different than that of healthy skin and have concerns about this assumption, and are concerned that the draft guidance document recommends the enrollment of "healthy volunteers with no history of previous skin disease or atopic dermatitis and with a healthy, homogeneous forearm..."[7]

The dermatology community is also concerned that the draft document fails to recognize the role that the inactive ingredients or vehicle may play in the delivery of a dermatologic drug. On healthy skin, petrolatum and urea are not active ingredients, but on scaly skin, such as psoriatic skin, they may be active and may have effects on the stratum corneum. Thus, varying the concentrations of so-called "inactive" ingredients may vary the overall effectiveness of the drug, regardless of the concentration of active drug in the stratum corneum as demonstrated in tape stripping. According to testimony presented by Dr. Jonathan Wilkin at the October 23rd meeting, "The vehicles are altering the stratum corneum. They can alter the apparent diffusion coefficient... the active has to partition from the vehicle into the stratum corneum and so

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[5] ***NIH Policy and Guidelines on the Inclusion of Children as Participants in Research involving Human Subjects;*** March 6, 1998.

[6] Shah, V; ***Advisory Committee for Pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee, Joint Meeting;*** Friday; October 23, 1998..

[7] Center for Drug Evaluation and Research; Food and Drug Administration: ***Guidance for Industry Topical Dermatological Drug Product NDAs and ANDAs - In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies;*** June 1998.

different vehicles can alter the partition coefficient quite dramatically. "[8] Therefore, if you test a psoriatic drug that was originally formulated as a crème and now have an ANDA that is in an ointment form with petrolatum as the inactive ingredient and you tape strip on healthy skin, can you assume that the drug is absorbed in the same manner? Can you make the same assumption for psoriatic skin?

And finally, we are concerned with anecdotal evidence that skin scientists are having some measure of difficulty in reproducing the tape stripping method as described in the FDA draft document. In correspondence to the Academy, Dr. John Voorhees, Chairman of the Department of Dermatology at the University of Michigan Medical School, Dr. Voorhees recounted the difficulties that his laboratory faced in replicating the skin tape stripping method as outlined by the FDA draft guidance. Dr. Voorhees wrote: "After we heard about the proposed FDA guidelines we did tape stripping using topical retinol and pooled the tape strips as recommended by the FDA. We used a standard organic solvent, which we typically use for HPLC. This solvent dissolved the gum from the tape as well as the drug.. .the dissolved material (a combination of drug and tape adhesive) was sticky and viscous. For this reason it could not be applied to the HPLC because this would have clogged the column. "[9] Dr. Voorhees also noted that his laboratory utilized Desquames tape discs for this procedure and noted that there was variability in weight from disc to disc that was often more than the weight of the stripped stratum corneum.[10] Elizabeth Duell, Ph.D., presented the work of Dr. Voorhees and his laboratory to the joint meeting on October 23, 1998."

The Academy continues to believe that skin tape stripping remains an intriguing, but still problematic testing method, and at this time should not be adopted as a means of assessing bioequivalence of generic dermatologic drugs. While the test maybe somewhat useful for assessing drugs with a site of action in the stratum corneum, such as anti-fungals or anti-virals, tape stripping is not a valid tool for assessing corticosteriods, anti-acne drugs or other therapies that act in the pilosebaceous unit. Assurance that generic drugs can reliably be substituted for innovator drugs is particularly important in light of the increasing use of restrictive formularies by third party payers. Given the times that we live in, we would do a disservice to our patients if we allowed the FDA to move forward with a one-size fits all leap of faith.

Sincerely,

Darrell S. Rigel, M.D.
President

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[8] Wilkin, J; ***Advisory Committee for Pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee, Joint Meeting;*** Friday; October 23, 1998.
[9] Voorhees, J; "Letter to Barbara Lowery of the American Academy of Dermatology"; August 10, 1998.
[10] Voorhees, J; "Letter to Barbara Lowery of the American Academy of Dermatology"; August 10, 1998.
[11] Duell, E; ***Advisory Committee for Pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Commitree, Joint Meeting;*** Friday; October 23, 1998.

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